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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 30 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 53 to 92 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 53 to 92 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

1) Claims 53 to 72 are pending in the instant application. Claims 1 to 52 have been canceled as requested by Applicant in Paper Number 8.

2) The numbering of claims is not accordance with 37 C.F.R. § 1.126. The original numbering of the claims must be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When claims are added, except when presented in accordance with 37 C.F.R. § 1.121(b), they must be renumbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 1 to 20 as submitted in Paper Number 8 have been renumbered 53 to 72, respectively.

3) Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120 as follows:

The continuing application must contain a specific reference to the parent application(s) in the first sentence of the specification as required by 37 C.F.R. § 1.78(A).

4) Claims 53, 57, 58 and 68 are objected to because they recite an improper Markush group. Specifically, these claims do not clearly identify the Markush element being claimed. Either "selected from" should be deleted from claim 58 or changed to "selected from the group consisting of" in which case the "or" in line 8 will need to be changed to "and". See M.P.E.P. 706.03(y).

The following is a quotation of the first paragraph of 35

U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5) The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure for the production of a DNA encoding a human neuronal nicotinic acetylcholine receptor subunit or a purified protein encoded thereby. The instant application discloses that Applicant has produced such a DNA but does not disclose how this DNA was made or might be made in such a clear and concise manner as to permit an artisan to reproduce this work without the need to resort to undue experimentation. The text on page 13 of the instant specification discloses that the DNAs of the instant invention were isolated by probing "various human cDNA libraries" with "analogous rat neuronal acetylcholine receptor subunit DNA fragments". This text does not disclose either the composition of the probes, the cell types or cell lines from which the cDNA libraries were created or the hybridization conditions under which the DNAs of the instant invention were made. The instant specification is, at best, only enabling for those DNAs encoded by the clones identified by the ATCC accession numbers presented on page 19 of the instant specification but the instant specification does not appear to indicate that all restrictions

on the availability to the public of this material will be irrevocably removed upon the granting of a patent as required by 37 C.F.R. 1.808. In the absence of such a statement the deposited material can not be relied upon to satisfy the requirements of 35 U.S.C. § 112, first paragraph, regarding enablement.

Claims 53 to 72 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

6) The specification is also objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure for the production of a substantially pure subunit of a human neuronal nicotinic acetylcholine receptor. The instant specification does not describe a purified subunit, disclose a method through which a subunit can be purified or identify a prior art reference which discloses such a method. Simple possession of a DNA encoding a particular protein does not place that protein in the hands of an artisan in a purified state.

Claims 55, 56 and 71 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

7) Claims 58 and 62 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 58 is incorrect because there is no antecedent basis for "the" alpha2, "the" alpha3 and "the" beta 2 subunit in lines 3, 6 and 9, respectively, of this claim in claim 54, from which it depends.

Claim 62 is incorrect because the phrase "wherein said cells eukaryotic" should be "wherein said cells are eukaryotic".

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

8) Claim 57 is rejected under 35 U.S.C. § 101 because it encompasses non-statutory subject matter. This claim appears to encompass a naturally occurring mRNA encoding a human neuronal nicotinic acetylcholine receptor.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9) Claims 53, 54, 57, to 60 and 63 are rejected under 35 U.S.C. § 102(a)as being clearly anticipated by the Fornasari et.al. publication (Neuroscience Letters 111:351-356, 06 April 1990, Applicant's reference AS).

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office

action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

10) Claims 53, 54, 57 to 63, 66 to 68, 70 and 72 are rejected under 35 U.S.C. § 103 as being unpatentable over the Boulter et.al. publication (P.N.A.S. 84: 7763-7767, Nov. 1987, Applicant's reference AG) in view of the Grenningloh et.al. (1R), Schofield et.al. (1S) and Noda et.al. (1T) publications. These claims are drawn to a substantially pure nucleic acid encoding an alpha or beta subunit of a human neuronal nicotinic acetylcholine receptor, cells containing and expressing that nucleic acid and a method of identifying a receptor ligand by using those cells. The Boulter et.al. publication described the isolation of nucleic

acids (cDNA) encoding an alpha 3, alpha 4 and beta 2 subunit of a rat neuronal nicotinic acetylcholine receptor (Figures 1 and 2), cells containing and expressing that nucleic acid and a method of identifying a receptor ligand by using those cells (Figure 3). The instant invention differs from the Boulter et.al. reference because the Boulter et.al. reference described nucleic acids encoding proteins of rat origin whereas the instant claims are drawn to nucleic acids encoding proteins of human origin.

Each of the Grenningloh et.al., Schofield et.al. and Noda et.al. publications described the isolation of a nucleic acid encoding a subunit of a human ligand-gated ion channel which is the class of receptor protein to which the receptor encoded by the nucleic acid of the instant invention belongs. The Grenningloh et.al. publication described the isolation of a human cDNA encoding a glycine receptor alpha subunit by using a DNA encoding a rat alpha subunit as a probe and disclosed on page 772 that the rat and human subunits "displayed very high homology (99%)". The Schofield et.al. publication described the isolation of DNAs encoding a human $GABA_A$ receptor alpha and beta subunit by using DNAs encoding their bovine counterparts as probes. The first paragraph of the RESULTS AND DISCUSSION section of this reference disclosed that the human alpha 1 subunit displayed 99% sequence identity with the bovine alpha subunit and the human beta subunit displayed 98% sequence identity with the bovine beta subunit. The Noda et.al. publication described the isolation of

a DNA encoding the alpha subunit of a human muscle nicotinic acetylcholine receptor by probing a cDNA library with a DNA encoding a bovine alpha subunit and disclosed at the beginning of page 821 that the human and bovine subunits shared 97% amino acid sequence homology. In fact, this reference disclosed that the amino acid sequence of the human subunit described therein was 80% identical to the sequence of an alpha subunit from a muscle nicotinic acetylcholine receptor from the eel Torpedo californica, indicating that the sequences of these subunits may be highly conserved between only distantly related animals. Additionally, the fourth sentence of the Grenningloh et.al. publication stated that "[b]y cDNA cloning, subunits of glycine and $GABA_A$ receptors were found to share significant sequence similarity and conserved transmembrane topology with subunits of the nicotinic acetylcholine receptor, an agonist-gated ion channel".

Because an artisan of molecular biology knew that the value of any neuroreceptor research such as that describe in the Boulter et.al. publication would ultimately lie in its applicability to human subjects that artisan would have found it obvious to have isolated nucleic acids encoding the human homologues of the rat neuronal nicotinic acetylcholine receptor subunits described therein by probing a human neuronal cDNA library with nucleic acid probes encoding the rat subunits using those methods described in each of the Grenningloh et.al.,

Schofield et.al. and Noda et.al. publications. That artisan would have known that this strategy had been successfully employed for the insolation of cDNAs encoding at least four structurally related proteins and would have been aware that the amino acid sequences of this type of protein had been shown to be very highly conserved (>95%) between mammalian species and that one member had been shown to be substantially conserved (80%) between human and eel. Given these facts that artisan would have had more than a reasonable expectation that such a strategy would work in this instance. For the reason stated above, the cells used to express the protein and the method of making such as claimed in claim 72 would also have been obvious because the skilled artisan would have found it obvious to produce such cells to permit the production and characterization of that receptor outside of its natural context by those methods which were well known in the art at that time and which was taught in each of these publications.

Claims 68 and 70 are specifically drawn to a method of identifying compounds which bind to a human neuronal nicotinic acetylcholine receptor which appears to be identical to the method described on page 7765 of the Boulter et.al. publication. Once an artisan had obtained nucleic acids encoding the human homologues of the rat neuronal nicotinic acetylcholine receptor subunits described therein they would have found it obvious to employ those nucleic acids in the ligand binding assay to

determine their pharmacological characteristics.

11) Claims 64, 65 and 69 are rejected under 35 U.S.C. § 103 as being unpatentable over the Boulter et.al., Grenningloh et.al., Schofield et.al. and Noda et.al. publications as applied to claims 53, 54, 57 to 63, 66 to 68, 70 and 72 above, and further in view of the Deschamps et.al. (Science 230:1174-1178, 1985, Applicant's reference AP) and Greenberg et.al. (1U) publications. These claims distinguish over those above by including a c-fos/CAT reporter plasmid in the cell containing nucleic acids encoding the receptor subunits. The Deschamps et.al. reference described the construction of a c-fos/CAT to detect the induced expression of the c-fos gene. The Greenberg et.al. publication disclosed that the stimulation of neuronal nicotinic acetylcholine receptors rapidly induced the transient expression of c-fos. Because c-fos induction was known to be one physiological consequence of ligand binding to a neuronal nicotinic acetylcholine receptor, an artisan would have found it obvious to include a c-fos/CAT reporter plasmid like that described in the Deschamps et.al. publication in a cell line expressing such a receptor from any source to allow for the detection of ligand binding to that receptor by detecting the expression of CAT.

12) Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm at telephone number (703) 308-4008. The examiner can

normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, G. D. Draper can be reached on (703) 308-4232. The fax phone number for this group is (708) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GARNETTE D. DRAPER
SUPERVISORY PATENT EXAMINER
GROUP 1800

John D. Ulm